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Dated 24 June 2003

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P01/7700 0.00-0217492.8

Request for grant of a patent

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29 JUL 2002

The Patent Office
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1. Your reference — SCH/HG/PU4903

2. Patent application number
(The Patent Office will fill in his part) — 0217492.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* — 07358700 3

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Method of Treatment

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* — 80725550006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	17 CF
Description	1
Claim(s)	1
Abstract	1
Drawings	5 only

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature S C Hockley Date 29-Jul-02

12. Name and daytime telephone number of person to contact in the United Kingdom: S C Hockley 01279 644355

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Novel Method of Treatment

This invention relates to a novel method of treatment using lamotrigine and novel formulations, in particular tablet formulations, for use in such methods.

Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine is disclosed in US 4,602,017 and EP0021121. Products comprising lamotrigine are marketed under the trade name LAMICTAL™ by the GlaxoSmithKline group of companies. Such products are particularly effective for treatment of CNS disorders, particularly epilepsy; pain; oedema; and psychiatric indications including bipolar disorder.

Various tablet formulations of lamotrigine have been approved for marketing, for instance, conventional compressed instant release (IR) tablets comprising 25 mg, 50mg, 100 mg, 150 mg or 200 mg of active ingredient. These are administered once, twice or three times daily. For lamotrigine, added to an antiepileptic drug regime containing valproic acid, titration begins at 25 mgs every other day for weeks 1 and 2 and increased to 25 mgs every day for weeks 3 and 4. After this initial period the maintenance dose of 100 to 400 mg/day can be achieved by increasing the dose by 25 to 50 mg/day. If lamotrigine is added to enzyme-inducing antiepileptic drugs (EIAEDS) without valproic acid the dose is 50 mg/day for weeks 1 and 2 and 100 mg/day in 2 divided doses thereafter. To achieve the maintenance dose of 300 to 500 mg/day in 2 divided doses, doses may be increased by 100 mg/day every 1 to 2 weeks. These regimens provide a therapeutic amount of lamotrigine.

In addition, WO92/13527 (The Wellcome Foundation Limited) describes tablet formulations comprising water dispersible tablets comprising lamotrigine and a dispersing agent where the dispersing agent is a swellable clay such as a smectite and is generally present within the granules of the tablet to provide a tablet which is capable of dispersing in water within 3 minutes to provide a dispersion which will pass through a 710 μm sieve. The tablet can be optionally film coated in which case the dispersion time is less than 5 minutes. Chewable dispersible tablets which may be swallowed whole, chewed or dispersed in a small amount of water are marketed comprising 2mg, 5mg, 25 mg or 100 mg of active ingredient. These are generally administered to paediatric patients.

WO96/17611 (The Wellcome Foundation Limited) discloses pharmaceutical compositions comprising

a) 0.5 to 50% by weight of lamotrigine;

b) from 15 to 50% by weight lactose;

c) from 15 to 50% by weight of starch;

d) from 0.5 to 50% crystalline cellulose; and

e) 5 to 15% by weight of polyvinylpyrrolidone;

and which is in the form of a free flowing powder having the following properties:

(i) no granules having a particle size of greater than 850μm,

(ii) at least 90% by weight having a particle size of 75 to 850 μm,

(iii) the granules disintegrate within 30 minutes according to the Disintegration Test of The Pharmacopoeia of Japan, 12th edition and

(iv) at least 90% by weight of lamotrigine dissolves within 30 minutes when the granules are subjected to the Dissolution Test, method 2 (paddle method) of The Pharmacopoeia of Japan 12th edition 1991.

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first pass metabolism. The absolute bioavailability is about 98%, which is not affected by food.

The chewable dispersible tablets were found to be equivalent to the lamotrigine compressed IR tablets whether they were administered as dispersed in water, chewed and swallowed or swallowed as whole in terms of rate and extent of absorption.

Existing marketed tablet formulations of lamotrgine are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. The peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The disadvantage is that the plasma concentration (pharmacokinetic profile (pk)) achieved with conventional tablets is cyclical, with peaks occurring after administration followed by troughs occurring before the next administration of drug, see Figure (1).

Until recently, it was not known where, in the gastrointestinal tract, lamotrigine is absorbed. In carrying out a regional absorption study it has recently been discovered that the extent of absorption of lamotrigine is consistent when the drug is delivered to any point in the gastrointestinal tract between the stomach and the ascending colon. The extent of absorption is also equivalent whether the drug is delivered as a solid or as a solution.

Accordingly, in a first aspect, the invention comprises a sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof.

A further aspect of the present invention provides for a method of treating CNS disorders, particularly epilepsy; pain; oedema and psychiatric conditions including bipolar disorder which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of a sustained release formulation.

A further aspect of the present invention provides for a method of treating CNS disorders, particularly epilepsy; pain; oedema and psychiatric conditions including bipolar disorder which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof, in the form of a sustained release formulation wherein the lamotrigine or a pharmaceutically acceptable derivative thereof is released approximately 2 to 20 hours after administration, preferably 6 to 16 hours after administration and more preferably 10 to 14 hours after administration.

When used herein the term "CNS disorders" includes epilepsy; pain; oedema and psychiatric conditions including bipolar disorder, particularly epilepsy, pain and bipolar disorder.

When used herein the term "pain" includes acute pain such as musculoskeletal pain, post operative pain and surgical pain, chronic pain such as chronic inflammatory pain (e.g. rheumatoid arthritis and osteoarthritis), neuropathic pain (e.g. post herpetic neuralgia, trigeminal neuralgia and sympathetically maintained pain) and pain associated with cancer and fibromyalgia or pain associated with migraine.

When used herein the term "pharmaceutically acceptable derivative" means a salt, ester or salt of such ester which upon administration to the recipient such a human is capable of providing (directly or indirectly) lamotrigine or an active metabolite thereof. Preferred salts are inorganic

acid salts such as hydrochloride, hydrobromide, phosphate or organic acid salts such as acetate, fumarate, xinafoate, tartrate, succinate or glutarate.

The term "treatment" as used herein includes the treatment of established disorders and also includes the prophylaxis thereof. This is particularly relevant for epilepsy wherein medication may treat seizures or prevent future seizures from occurring.

As used herein, the term "sustained release" refers to the gradual but continuous release over a relatively extended period of lamotrigine after oral ingestion e.g. 2-20 hours preferably between 6 to 16 hours, and more preferably between 10 and 14 hours and which starts when the formulation reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may throughout the small intestine and after the formulation reaches the large intestine.

A further aspect of the invention provides a method of treating CNS disorders which comprises orally administering to a patient a therapeutically effective amount of lamotrigine in the form of a sustained release formulation wherein the lamotrigine is released from the formulation in the 2 to 20 hours after administration, preferably 6 to 16 hours after administration and more preferably 10 to 14 hours after administration

A further aspect of the invention provides a sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof, wherein the lamotrigine or a pharmaceutically acceptable derivative thereof is released from the formulation 2 to 20 hours after administration, preferably 6 to 16 hours after administration and more preferably 10 to 14 hours after administration.

Administration of lamotrigine over this time period delivers it gradually to the sites where lamotrigine is readily absorbed thereby promoting an area under the curve (AUC) equivalent to the instant/immediate release (IR) tablet (90% confidence interval (CI) for the geometric least squares (GLS) mean ratio should fall within the range 80-125% compared to the reference IR product).

Suitably the formulations are preferably formulated such that the release of the active substance is predominantly in the stomach, small intestine and into the colon.

In a further aspect, the invention provides a method of treating CNS disorders, which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of sustained release formulation wherein the lamotrigine is present in the range of 1 to 500 mg, preferably 25 to 400mg.

Preferably the sustained release formulation comprises an amount of lamotrigine selected from 25mg, 50mg, 100mg, 200mg or 400mg.

Preferably the sustained release formulation is administered in a dosage regimen which is sufficient to maintain control over the disorder.

Preferably the dosage regimen is once a day.

An advantage of sustained release formulations is increased patient compliance.

Socio-economic factors do not influence compliance: non-compliance is just as likely in wealthy, well educated, and healthy patients as it is in patient outside these categories. In most cases, epilepsy is a life-long disease that requires consistent and adequate antiepileptic drug (AED) blood levels to maximize seizure control. Further, it is generally accepted that each additional seizure may increase the risk of recurrence and worsen the overall prognosis.

Therefore, primary treatment objectives for patients with epilepsy are maintenance of adequate AED levels and prevention of subsequent seizures. Compliance with the prescribed dosing regimen is essential for the maintenance of therapeutic blood levels.

Patients with epilepsy often are treated with polypharmacy. Patients with severe or refractory epilepsy frequently require the co-administration of two or more AEDs to achieve adequate seizure control. Also, it is not unusual for patients to have other concurrent chronic medical conditions such as depression, heart conditions or diabetes that also require adherence to daily dosing regimens.

Preferably the formulation provides about a 10 to 20% reduction in Cmax over the Cmax obtain in the same patient on an IR dose if administered once daily.

Preferably the formulation provides a time to Cmax (t_{max}) of 10 to 16 hours post dose.

Preferably the formulation provides a rate of increase to t_{max} of less than 50% of an individual IR dose.

Preferably the formulation provides at 24 hours post dose a mean minimum serum concentration (Cmin) of at least 80 to 125% compared to the same IR dose in the same patient.

Preferably the formulation provides a fluctuation index (Cmax-Cmin/Cave) in the range of 0.15 to 0.45.

A further aspect of the invention is a method of treating epilepsy comprising orally administertion to a patient of a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of a sustained release formulation

A further aspect of the invention is the use of lamotrigine or a pharmaceutically acceptable derivative thereof for manufacture of a sustained release formulation for the treatment of CNS disorders.

A further aspect of the invention is the use of lamotrigine or a pharmaceutically acceptable derivative thereof for the treatment of CNS disorders.

The dosage in a sustained release formulation intended to be swallowed whole where the dosage form integrity is essential for controlling the rate of release may conveniently be provided as a number of swallow tablets or capsules, for instance two, three or four. In cases where the release is achieved from a number of discrete particles, beads or granules, the dosage form need not be swallowed intact as long as the beads or particles themselves remain intact.

The dosage in a sustained release formulation may be also provided as a single tablet.

Preferably, a sustained release formulation of the present invention has an *in vitro* dissolution profile in which 45 to 65%, preferably 45 to 55% of the lamotrigine content is dissolved between 3 to 8 hours, most preferably between 4 to 6 hours; and that 90% of lamotrigine is dissolved between 6 and 16 hours, most preferably between 10 to 14 hours. In comparison, a conventional, immediate release lamotrigine tablet dissolves 80% within 30 minutes. The dissolution profile may be measured in a standard dissolution assay, for instance <711> Dissolution Test, Apparatus 1 or 2 or 3 or 4, provided in USP 24, 2000 and updated in subsequent supplements, at 37.0 ± 0.5°C, using dilute hydrochloric acid or other suitable media (900 ml) and a paddle speed of 50-75 rpm.

Preferably, the sustained release formulation provides an *in vivo* "Area Under the Curve" (AUC) value which is equivalent to that of the existing conventional tablet, for instance at least 80%, preferably at least 90% to 110%, more preferably about 100%, but not exceeding 125% of

that of the corresponding dosage of lamotrigine taken as a conventional (immediate release) formulation, over the same dosage period, thereby maximising the absorption of lamotrigine from the sustained release formulation.

The pharmcokinetic profile for a dosage of the present invention may be readily determined from a single dosage bioavailability study in human volunteers. Plasma concentrations of lamotrigine may then be readily determined in blood samples taken from patients according to procedures well known and documented in the art.

The person skilled in the art will appreciate that a therapeutically effective amount will depend on the patient's age, size, severity of disease and other medication.

Preferred sustained release formulations are ultimately functional coated tablets or caplets, wax or polymer containing tablets or caplets or time-release matrices, or combinations thereof. They can also be controlled release beads, granules, spheroids that are contained within a capsule or administered from a sachet or other unit dose powder device.

Representative sustained release formulations include a tablet, including swallow tablets, a capsule, granules or a sachet, typically a swallow tablet which may or may not be coated.

A further aspect of the invention is a formulation comprising lamotrigine or a pharmaceutically acceptable derivative thereof and a release retarding excipient which allows for sustained release of lamotrigine or a pharmaceutically acceptable derivative thereof. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark) polymers, for example Eudragit L (trade mark) which may be used either alone or with a plasticiser; release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents; polymeric materials which form a gel on contact with water or aqueous media; and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

These sustained release formulations are often referred to in the art, as "matrix formulations" where by the drug is incorporated into a hydrated polymer matrix system and is released via diffusing or erosion, for example WO98/47491 and US 5,242,627.

Release retarding polymers which have a high degree of swelling include, *inter alia*, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxyethylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, hydroxyethyl cellulose high-molecular weight polyvinylalcohols etc.

Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, hydroxyethyl cellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

Preferably the release retarding polymer used has a molecular weight in the range 5 to 95, more preferably in the range 10 to 50.

A preferred release-retarding polymer is one of the available grades of hydroxypropylmethyl cellulose or hydroxyethyl cellulose.

Examples of other polymers which may be used include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100LV (Trade Mark), POLYOX WSR N-80 or mixtures thereof.

Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, carbohydrate-based substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenin, soluble and insoluble alginates, carboxypolymethylene, casein, zein, and the like, and proteinaceous substances such as gelatin.

Preferably the release-retarding polymer is Methocel E4MP Grade, POLYOX WSR N-80, Methocel K100LV. Such a sustained release formulation may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.

The sustained release formulation may also include diluents such as lactose; compression aids such as microcrystalline cellulose, dicalcium phosphate, sucrose, mannitol, xylitol; starches, and lubricants such as magnesium stearate, sodium stearyl fumarate, stearic acid. The sustained release formulation may further comprise disintegrants, such as cross-linked polyvinylpyrrolidone (CLPVP) and sodium starch glycollate; binders such as povidone (polyvinylpyrrolidone); flow aids such as silicon dioxide or talc. Typically, the sustained release formulation comprises from about 2.5 to 80% by weight of lamotrigine; from 0 to 70 % by weight of diluent/compression aid and from 1 to 2.5 % by weight of lubricant.

Preferably the release retarding polymer is present in a range of 10 to 70 % by weight polymer.

Preferably the sustained release formulation comprises 2.5 to 80% by weight lamotrigine or a pharmaceutically acceptable derivative thereof.

In a preferred embodiment the sustained release formulation comprises

a) to 2.5 to 80% by weight lamotrigine or a pharmaceutically acceptable derivative thereof;
b) to 17.5 to 70% by weight slow release polymer;
c) to 0 to 60 % by weight diluent;
d) to 0 to 20 % by weight compression aid; and
e) to 0.1 to 2.5% by weight lubricants.

In a preferred embodiment the sustained release formulation comprises

a) to 2.5 to 80% by weight lamotrigine or a pharmaceutically acceptable derivative thereof;
b) to 17.5 to 70% by weight slow release polymer;
c) to 0 to 60 % by weight diluent; and
d) to 0.1 to 2.5% by weight lubricants.

More preferably the sustained release formulation comprises

a) to 8.3 to 50 % by weight lamotrigine or a pharmaceutically acceptable derivative

thereof;

b) to 17.5 to 66.3 % by weight Methocel E4MP, CR Grade, POLYOX WSRN-80 or Methocel, K100LV or a mixture thereof;

c) to 25 to 60 % by weight lactose; and

d) to 0.1 to 0.4 % by weight magnesium sterate.

A further aspect of the invention is a formulation comprising lamotrigine or a pharmaceutically acceptable derivative thereof and a release retarding coating on one or more of the outer surfaces of a tablet or a bead. A conventional instant release compression tablet may be at least partially coated by a release retarding coating or alternatively, a pharmaceutically acceptable bead is used in which the lamotrigine is incorporated and then the bead is at least partially coated by a release retarding coating. The use of beads allows flexibility in a dosage regimen because a dose can be measured to suit a patient's requirements.

The film coat may act as a semi permeable barrier thereby allowing diffusion control of drug release by water insoluble polymer, or a partially water-soluble polymer. Alternatively the film coating may control the dissolution rate. Such film coating may, for example, be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media or biological liquids. Suitably the film coat should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium.

Suitable polymers for the film coat include acrylates, methacrylates, copolymers of acrylic acid or its esters, celluloses and derivatives thereof such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohol etc. Film coats comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The film coat may itself contain lamotrigine, for example the film coat may be a slow or delayed release layer. Film coats may typically have an individual thickness of 2 microns to 10 microns.

Suitable polymers for film coats which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, Eudragit (trade mark) polymers, Aquacoat (trade mark) and hydroxypropylmethyl cellulose used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Alternatively and more preferred the film coat may be compressed. A preferred polymer is SURELEASE (trade mark) an aqueous ethylcellulose dispersion (E-7-19010).This can be obtained from COLORCON a division of Berwind Pharmaceuticals Services Inc. Additionally a mixture of SURELEASE polymer and a pore forming material for example OPADRY (trade mark) clear (YS-2-7013), again which can be obtained from COLORCON, can be used. One range which can be used is 3 to 5% by weight of coating on a tablet.

Additional embodiments have a 50% to 80% by weight of film coating of SURELEASE polymer and 50% to 20% by weight of film coating of OPADRY.

A plasticiser such as hydrogenated castor oil may be combined with the polymer. The film coating may also include conventional binders, fillers, lubricants, colourants such as iron oxides or organic dyes and compression aids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

A further aspect of the invention is a formulation comprising lamotrigine or a pharmaceutically acceptable derivative thereof and an osmotic agent which is coated with a water permeable membrane containing at least one hole. The active ingredient is "pumped" out of the tablet through the hole in the water permeable membrane. Examples of osmotic pump formulations of other drugs are contained in WO95/29665.

A further particular aspect of the invention provides a system for the sustained release of lamotrigine or a pharmaceutically acceptable derivative thereof, comprising (a) a deposit-core comprising an effective amount of the active substance and having defined geometric form, and (b) a support-platform applied to said deposit-core, wherein said deposit-core contains at least the active substance, and at least one member selected from the group consisting of (1) a polymeric material which swells on contact with water or aqueous liquids and a gellable polymeric material wherein the ratio of the said swellable polymeric material to said gellable polymeric material is in the range 1:9 to 9:1, and (2) a single polymeric material having both swelling and gelling properties, and wherein the support-platform is an elastic support, applied to said deposit-core so that it partially covers the surface of the deposit-core and follows changes due to hydration of the deposit-core and is slowly soluble and/or slowly gellable in aqueous fluids. The support-platform may comprise polymers such as hydroxypropylmethylcellulose, plasticizers such as a glyceride, binders such as polyvinylpyrrolidone, hydrophilic agents such as lactose and silica, and/or hydrophobic agents such as magnesium stearate and glycerides. The polymer(s) typically make up 30 to 90% by weight of the support-platform, for example about 35 to 40%. Plasticizer may make up at least 2% by weight of the support-platform, for example about 15 to 20%. Binder(s), hydrophilic agent(s) and hydrophobic agent(s) typically total up to about 50% by weight of the support-platform, for example about 40 to 50%.

Tablet formulations of the invention may contain a waxy or similar water insoluble material in order to form matrix. Such a tablet may be formed by dry blending the drug and any diluent materials with the waxy material in particulate form. Examples of suitable waxy materials are cetyl alcohol, steryl alcohol, palmitoyl, alcohol, oleyl alcohol, carnuba wax. There resulting blend is then compressed into tablets using conventional tablet making technologies. An alternative methods of manufacturing these tablets would be to granulate the drug with the diluent materials with a suitable volatile granulating fluid (water, ethanol, isopropanol) and to dry the granules, then coat them with a molten waxy material. The resultant granules are then compressed into tablet using conventional tablet making technology.

Granule based tablets can also be made by spraying a solution or suspension of one of the methacrylate based release controlling agents (Eudragit – trade mark) onto a blend of the drug mixed with one of the common diluents. Examples of suitable Eudragits are NE30D, L, S. The granules formed in the process are then dried and compressed using conventional tablet making technology.

The tablet formulations of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture or damage to the tablet. The

protective layer may itself contain active material content, and may, for example, be an immediate release layer, which immediately disintegrates in contact with water or aqueous media. Preferred materials for the protective layer are hydroxypropylmethylcellulose and polyethylene glycol, with titanium dioxide as an opacifying agent, for instance as described in WO 95/28927 (SmithKline Beecham).

As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer. A suitable buffer is calcium hydrogen phosphate.

The protective layer, if present, may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the protective layer material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, e.g. by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally, or alternatively, the first and second layers may be formed and a barrier layer may then be formed, for instance by compression, spraying or immersion, on one or more of the end faces of the tablet.

Chewable tablets according to the present invention typically comprise a chewable base formed from, for instance, mannitol, sorbitol, dextrose, fructose, lactose, xylitol, maltitol, sucrose, or galactose alone or in combination. A chewable tablet may also comprise further excipients, for instance, disintegrants, lubricants, sweetening agents, colouring and flavouring agents. Such further excipients together will preferably comprise from 3 to 10%, more preferably 4 to 8%, yet more preferably 4 to 7% by weight of the tablet. Disintegrants may be present in from 1 to 4%, preferably from 1 to 3%, more preferably from 1 to 2% by weight of the tablet. Representative disintegrants include crospovidone, sodium starch glycollate, starches such as maize starch and rice starch, croscarmellose sodium and cellulose products such as microcrystalline cellulose, microfine cellulose, low substituted hydroxy propyl cellulose, either used singly or in admixture. Preferably, the disintegrant is crospovidone. Lubricants may be present in from 0.25 to 2.0%, preferably from 0.5 to 1.2% by weight of the tablet. Preferred lubricants include magnesium stearate. Preferably, the sweetening agent is an artificial sweetening agent such as sodium saccharin or aspartame, preferably aspartame, which may be present in from 0.5 to 1.5% by weight of the tablet. Preferably, a tablet of the present invention is substantially free of sugar (sucrose). Preferred flavouring agents include fruit flavours which may be natural or synthetic, for instance peppermint, cherry and banana, or a mixture thereof.

Single dose sachets according to the present invention comprise, in addition to the drug substance, excipients typically included in a sachet formulation, such as a sweetener, for instance aspartame, flavourings, for instance fruit flavours, optionally a suspending agent such as xanthan gum, as well as silica gel, to act as a desiccant.

Capsules according to the present invention comprise, in addition to the drug substance, excipients typically included in a capsule, for instance starch, lactose, microcrystalline cellulose, ethyl cellulose, magnesium stearate. Preferably, capsules are prepared from materials such as HPMC or a gelatin/PEG combination. Preferably the capsules will contain beads or granules. These beads or granules are composed of the drug substance in a concentration of between 5% and 95%, preferably 20 to 80%, most preferably 50 to 80%. The drug substance is mixed with a

suitable granulating aid such as microcrystalline cellulose, lactose, and granulated using a suitable granulating fluid such as water, ethanol, isopropanol. The wet granules are forced through small orifices of 0.5mm to 3 mm diameter then spheronised into discrete particles using a rapidly spinning disc. The spherical particles are then dried and coated with a release controlling film coat containing for example ethyl cellulose, pH sensitive or insensitive methacrylic acid copolymers and their derivatives. The coated particles are filled into suitable capsule shells.

Preferably, the unit dosage forms of the present invention are packaged in containers that inhibit the ingress of atmospheric moisture, for instance blister packs, tightly closed bottles or desiccated pouch packs etc which are conventional in the art. Preferred bottles include HDPE bottles.

Other sustained release formulations which may be suitable for incorporating lamotrigine or other suitable derivatives thereof are described in:

Sustained Release Medications, Chemical Technology Review No. 177. Ed. J.C. Johnson. Noyes Data Corporation 1980.

Controlled Drug Delivery, Fundamentals and Applications, 2nd Edition. Eds. J.R. Robinson, V.H.L. Lee. Mercel Dekkes Inc. New York 1987.

Examples of delayed release formulations which are suitable for incorporating lamotrigine or other suitable derivatives thereof are described in:

Remington's Pharmaceutical Sciences 16th Edition, Mack Publishing Company 1980, Ed. A. Osol.

A further aspect of the invention is a sustained release formulation of the invention additionally containing a second active ingredient selected from carbamazepine, valproic acid, gabapentin, diazepam, phenytoin, bupropion or paroxetine HCl.

Preferably both the lamotrigine and the second active ingredient are both administered in a sustained release fashion. Alternatively the formulation contains 2 phases, one sustained release phase comprising lamotrigine and a second instant release phase comprising the second active ingredient.

The invention will now be described by way of example only, with reference to the accompanying drawings, in which:

Figure 1 Simulated lamotrigine pharmacokinetic profile for 200mg lamotrigine IR tablets administered twice daily.

Figure 2. Dissolution profile of three different batches of lamotrigine 150mg IR tablets.

Figure 3 Dissolution profiles from a matrix tablet from Example 1.

Figure 4. Dissolution profiles from a film coated tablet from Example 3.

A further aspect of the invention is a sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof which has an *in vitro* dissolution profile substantially similar to the dissolution profile shown in Figure 3 or 4.

The present invention also extends to formulations which are bioequivalent to the tablets of formulations, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

Example 1 – Matrix formulations

Example 1 a) Matrix Tablets with 35% Polymer

(Polymers are either Methocel E4MP CR, Methocel K100 LV, Polyox WSR N-80)

Component	Quantity (mg/tablet)	Quantity (%w/w)
Lamotrigine	150	30.0
Lactose (Fast-Flo)	35	7.0
Microcrystalline cellulose	138	27.6
Polymer	175	35.0
Magnesium Stearate	2	0.4
Total Tablet Weight	500	100

Bulk Preparation Method

First the components are weighed from bulk containers in the following amounts:

Ingredients	Amount (G)
Lamotrigine	450.0
Lactose (Fast-Flo)	105.0
Microcrystalline cellulose	414.0
Polymer	525.0
Magnesium Stearate	6.0

The components are then sieved using a Russel-SIV equipped with a 20-mesh (850μm) or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The lamotrigine, lactose, microcrystalline cellulose and polymer are blended for 15 minutes using a suitable blender, such as a Matcon-Buls bin-type blender, a V-blender or equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary tablet press, typically a Fette 2090 or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

Example 1b) Matrix Tablets with 25% Polymer

(Polymers are either Methocel E4MP CR, Methocel K100 LV, Polyox WSR N-80)

Component	Quantity (mg/tablet)	Quantity (%w/w)
Lamotrigine	150	30.0
Lactose (Fast-Flo)	85	17.0
Microcrystalline cellulose	138	27.6
Polymer	125	25.0
Magnesium Stearate	2	0.4
Total Tablet Weight	500	100

Bulk Preparation Method

First the components are weighed from bulk containers in the following amounts:

Ingredients	Amount (G)
Lamotrigine	450.0
Lactose (Fast-Flo)	255.0
Microcrystalline cellulose	414.0
Polymer	375.0
Magnesium Stearate	6.0

The components are then sieved using a Russel-SIV equipped with a 20-mesh (850μm) or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The lamotrigine, lactose, microcrystalline cellulose, and polymer are blended for 15 minutes using a suitable blender, such as a Matcon-Buls bin-type blender, a V-blender or equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary tablet press, typically a Fette 2090 or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

Example 1c) Matrix Tablets with 15% Polymer

Polymers are either Methocel E4MP CR, Methocel K100 LV, Polyox WSR N-80

Component	Quantity (mg/tablet)	Quantity (%w/w)
Lamotrigine	150	30.0
Lactose (Fast-Flo)	35	7.0
Microcrystalline cellulose	238	47.6

Polymer	75	15.0
Magnesium Stearate	2	0.4
Total Tablet Weight	500	100

Bulk Preparation Method

First the components are weighed from bulk containers in the following amounts:

Ingredients	Amount (G)
Lamotrigine	450.0
Lactose (Fast-Flo)	105.0
Microcrystalline cellulose	714.0
Polymer	225.0
Magnesium Stearate	6.0

The components are then sieved using a Russel-SIV equipped with a 20-mesh (850μm) or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The lamotrigine, lactose, microcrystalline cellulose and polymer are blended for 15 minutes using a suitable blender, such as a Matcon-Buls bin-type blender, a V-blender or equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary tablet press, typically a Fette 2090 or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

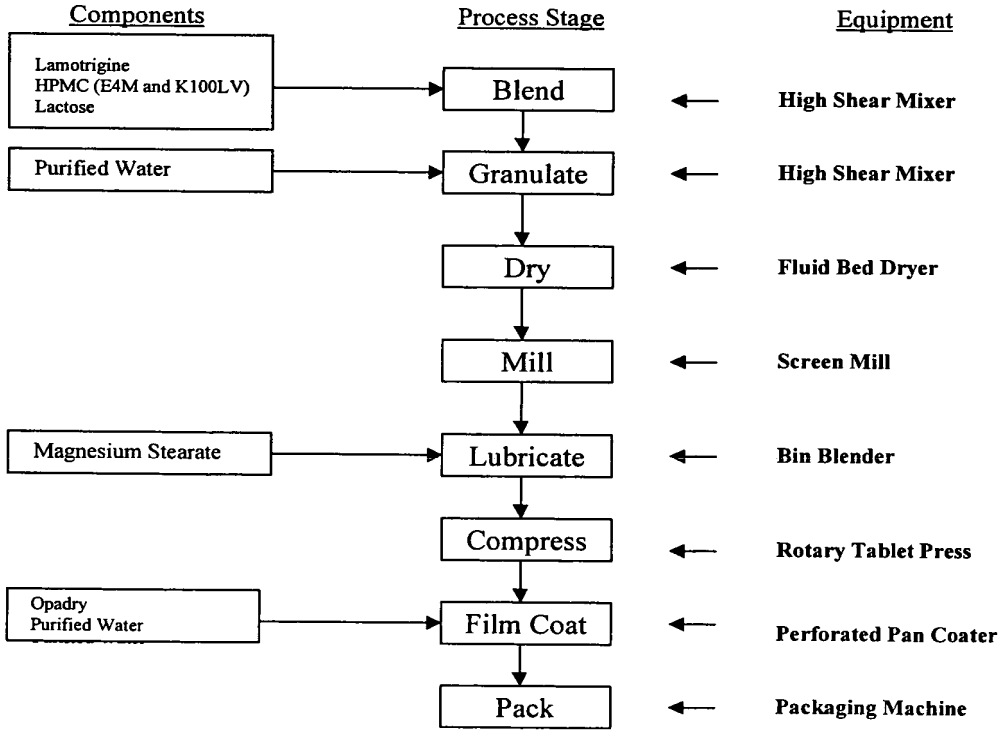
Example 2 Matrix Formulations

Strength	25 mg		50 mg		100 mg		200 mg	
Excipient	Slow	Fast	Slow	Fast	Slow	Fast	Slow	Fast
Lamotrigine	25 mg (12.5%)	25 mg (12.5%)	50 mg (25%)	50 mg (25%)	100 mg (33.3%)	100 mg (33.3%)	200 mg (50%)	200 mg (50%)
E4M	55.75	20%	30%	10%	25%	2.5%	15%	5%
K100LV	9.75	20%	20%	25%	10%	25%	5%	15%
Lactose*	qs	Qs	qs	q.s.	qs	qs	qs	qs
Mg Stearate	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Tablet Weight (mg)	300	300	325	325	350	350	400	400

* qs = the mass balance to achieve the target tablet weight

In the above table slow represents tablets where 90% of the lamotrigine dissolved in 16 hours, fast represents 90% of the lamotrigine dissolved in 6 hours
The formulations as described in Example 2 are prepared as set out in the flow diagram below.

Flow Diagram of the Manufacturing Process for Lamictal SR



Example 3 Film coating formulations

Surelease with Opadry

Component	Quantity (mg/tablet)	Quantity (%w/w)
Lamotrigine	150	30.0
Microcrystalline cellulose	345	69.0
Magnesium Stearate	5	1.0
Total Tablet Weight	500	100

Bulk Preparation Method

First the components are weighed from bulk containers in the following amounts:

Ingredients	Amount (KG)
Lamotrigine	4.5
Microcrystalline cellulose	10.35
Magnesium Stearate	0.15

The components are then sieved using a Russel-SIV equipped with a 12 mesh (850μm) or an equivalent sieve and mesh, and deposited into a stainless-steel blending container.

The lamotrigine and microcrystalline cellulose are blended for 15 minutes using a suitable blender, such as a Matcon-Buls bin-type blender, a V-blender or equivalent. The magnesium stearate is then added to the mixture and blending is continued for approximately 2 minutes.

The lubricated blend is then compressed using a suitable rotary tablet press, typically a Fette 2090 or equivalent. In-process controls for tablet weight and hardness are applied at appropriate intervals throughout the compression run and adjustments to the tablet press are made as necessary.

The tablets are then film-coated using O'Hara LabCoat II, or equivalent coater. Tablets are sprayed with a solution of Surelease and Opadry at either a 50/50 (solution A) or an 80/20 ratio (solution B). The aqueous coating solutions, A and B, are described below. Tablets were coated up to a 5% theoretical weight gain.

Coating Solution A

Weight out 162.5 grams of Surelease (E7-19060) and 162.5 g of Opadry (YS-2-7013) and placed into a suitable stainless steel mixing tank. Add 2437.5 grams of water. Mix until uniformed. Stir continually during application.

Coating Solution B

Weight out 260.00 grams of Surelease (E7-19060) and 65.00 g of Opadry (YS-2-7013) and placed into a suitable stainless steel mixing tank. Add 1061.67 grams of water. Mix until uniformed. Stir continually during application.

Figure 4 shows the dissolution profiles for tablets coated with coating solution B for 3% and 5% weight gain. Both, on average were greater than 90% dissolved after 3 hours.

Example 4

Pharmacokinetic study to investigate lamotrigine sustained release formulation in humans:

The in vivo disposition of the lamotrigine sustained release formulation will initially be assessed in a healthy volunteer pharmacokinetic study. The study will be of incomplete block design consisting of 2 doses (e.g., 25 mg (granule strength 1) and 200 mg (granule strength 2)) and 3 different SR release rates at each dose, with the IR formulation as a reference. Each volunteer will participate in 4 out of the possible 7 arms/formulations. For each formulation, blood samples will be collected from each volunteer over a specified period of time for the measurement of lamotrigine serum concentrations and, consequently, the derivation of lamotrigine pharmacokinetic parameters. Safety and tolerability of each formulation will also be assessed.

A further aspect of the invention is a pharmaceutical formulation as described in any one of examples 1 to 3.

Tradename	Generic description	Supplier
Methocel E4M CR	hydroxpropyl methylcellulose 28-30% (nominal viscosity, 2% in water, of 4000mPa s)	Dow
Methocel K4M	hydroxpropyl methcellulose 19-24% methoxyl, 4000mPa s nominal viscosity (2% in water),	Dow
Methocel E5	hydroxpropyl methcellulose 28-30%19-24% methoxyl, 5000mPa s nominal viscosity (2% in water),	Dow
Opadry (YS-2-7013)	hyrdoxypropylmethylcellulose aqueous dispersion	Colorcon
Surelease (E-7-19010)	aqueous ethylcellulose dispersion	Colorcon
Eudragit® L30D-55	methacrylic acid copolymer	Rohm Pharma)

Eudragit® RS 30D Eudragit® RL 30D	ammonio-methacrylic copolymer RL=10% quat. ammonium RS=5% quat. ammonium	(Rohm Pharma)
Aquacoat	ethylcellulose latex suspension	(FMC)

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

Claims

1. A method of treating CNS disorders, particularly epilepsy; pain; oedema and psychiatric conditions including bipolar disorder which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of a sustained release formulation.

2. A method of treating CNS disorders, which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of sustained release formulation wherein the lamotrigine or a pharmaceutically acceptable derivative is present in the range of 1 to 500 mg.

3. A method of treating CNS disorders which comprises orally administering to a patient a therapeutically effective amount of lamotrigine in the form of a sustained release formulation wherein the lamotrigine is released from the formulation in the 2 to 20 hours after administration

4. A method of treatment of CNS disorders which comprises orally administering to a patient a therapeutically effective amount of lamotrigine or a pharmaceutically acceptable derivative thereof in the form of a sustained release formulation once a day.

5. A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof.

6. A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof, wherein the lamotrigine or a pharmaceutically acceptable derivative thereof is released from the formulation 2 to 20 hours after administration.

7. A sustained relative formulation of lamotrigine or a pharmaceutically acceptable derivative thereof which has an *in vitro* dissolution profile in which 45 to 65 % of the lamotrigine as dissolved in 4-6 hours.

8. A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof which has an *in vitro* dissolution profile substantially similar to the dissolution profile shown in Figure 3 or 4.

9. A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof wherein the formulation is an enteric coated tablet or caplet, wax or polymer coated tablet or caplet, time release matrix or combination thereof.

Abstract

A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof.

Figures

Figure 1 – Simulated lamotrigine pharmacokinetic profile for 200mg lamotrigine (Lamictal™) dose administered twice daily.

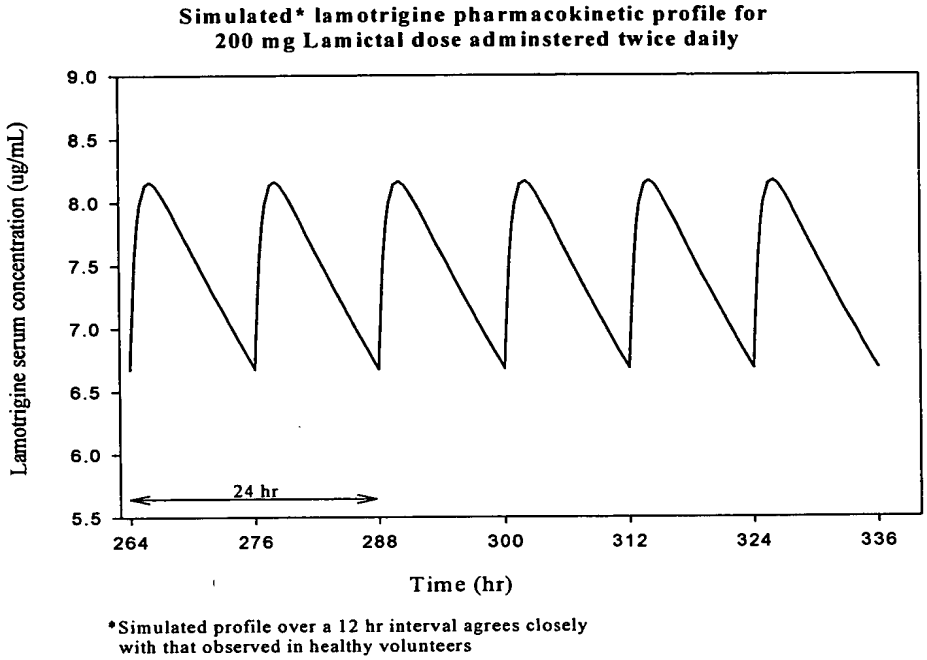


Figure 2. Dissolution profile of three different batches of lamotrigine (Lamictal™) 150mg tablets.

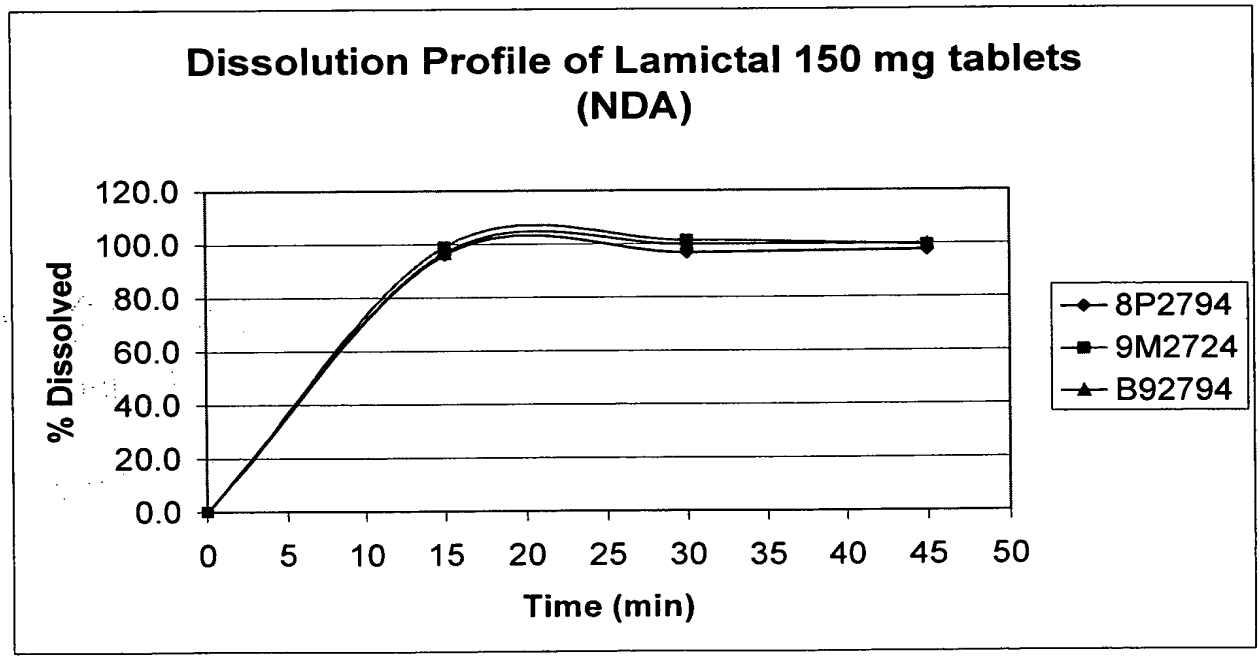
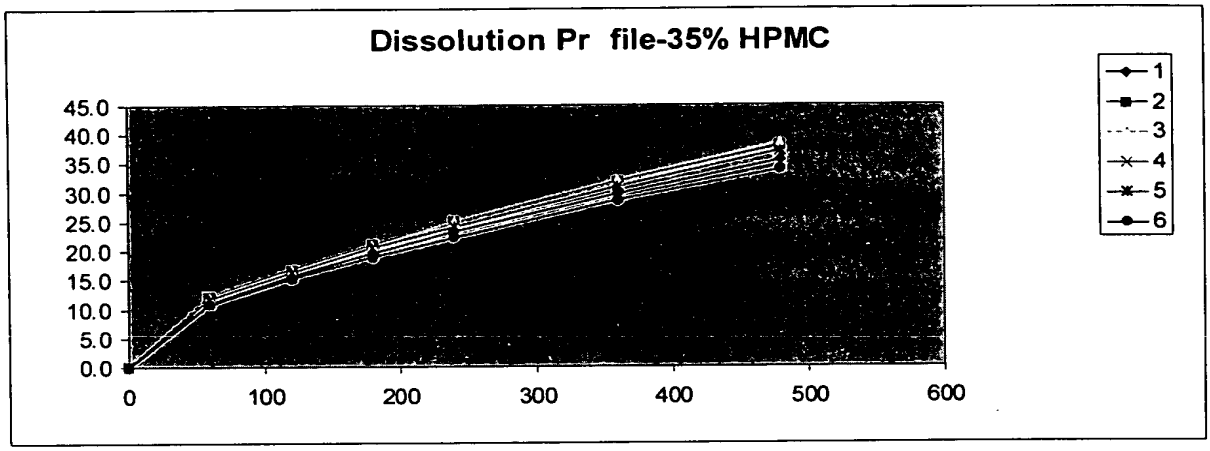
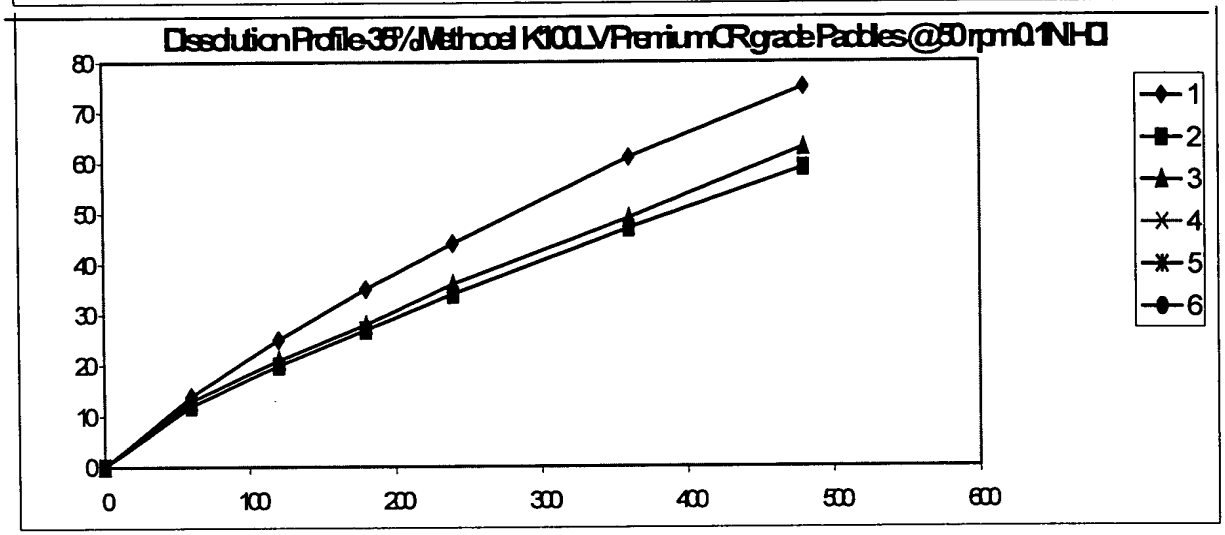


Figure 3a Matrix Tablet with 35% Polymer


Dissolution Pr file-35% HPMC
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0
100
200
300
400
500
600
1
2
3
4
5
6


80
70
60
50
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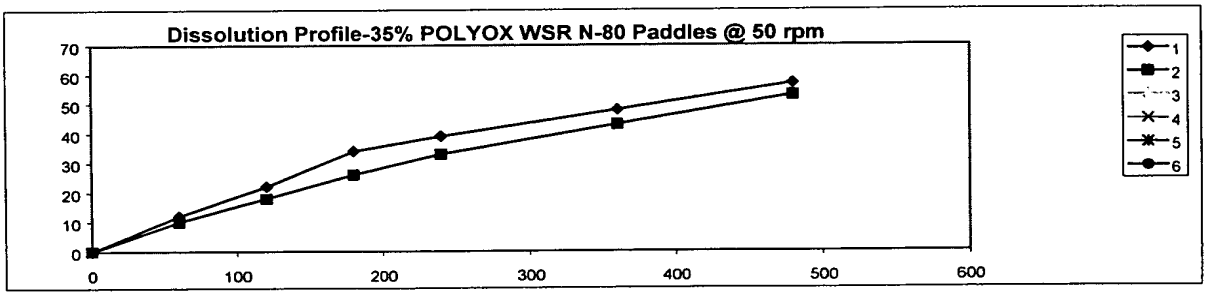
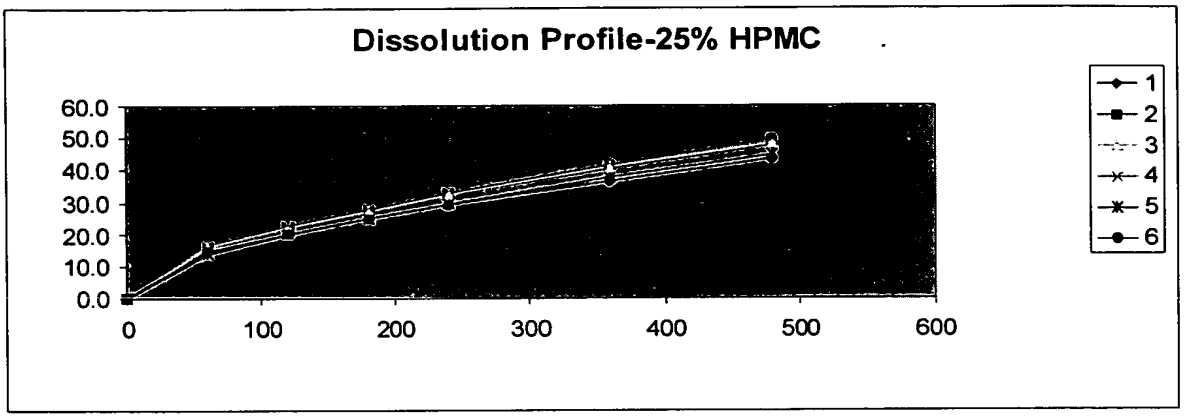
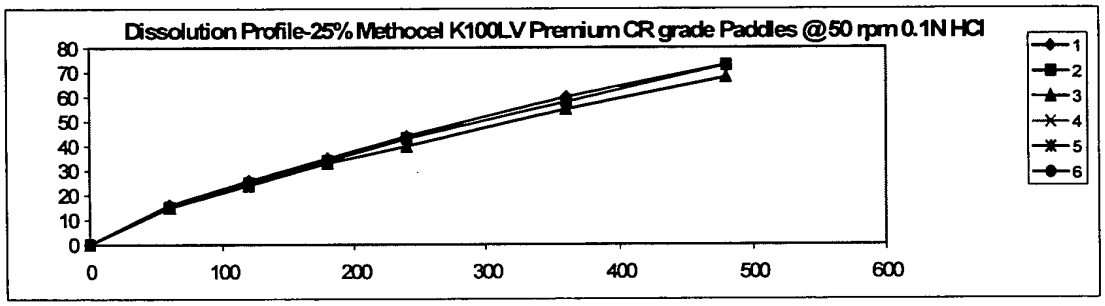

Dissolution Profile-35% POLYOX WSR N-80 Paddles @ 50 rpm
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
1
2
3
4
5
6

5

Figure 3b) Matrix Tablets with 25% polymer





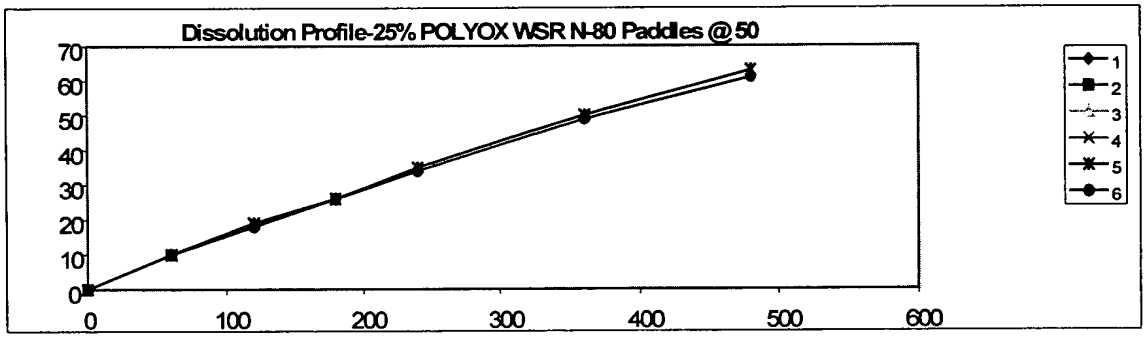
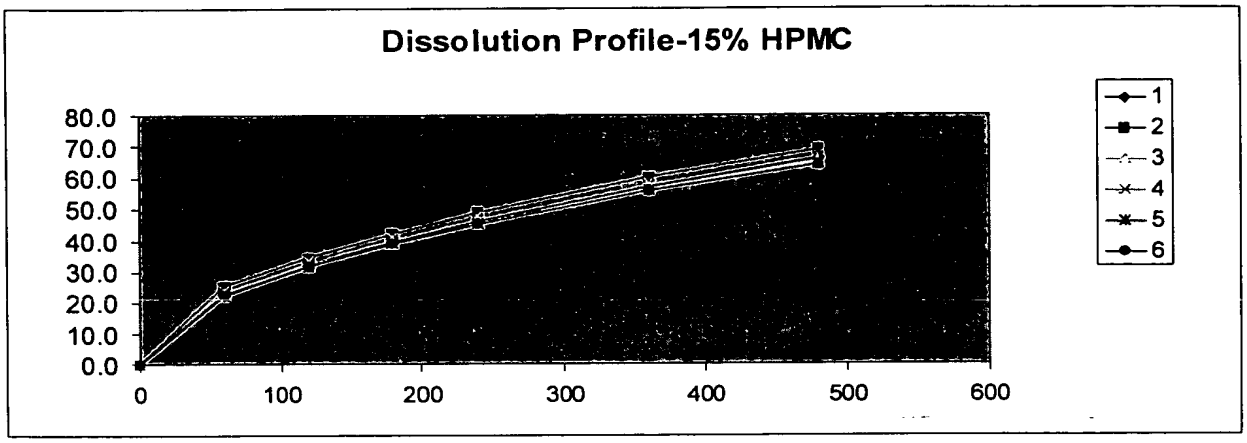
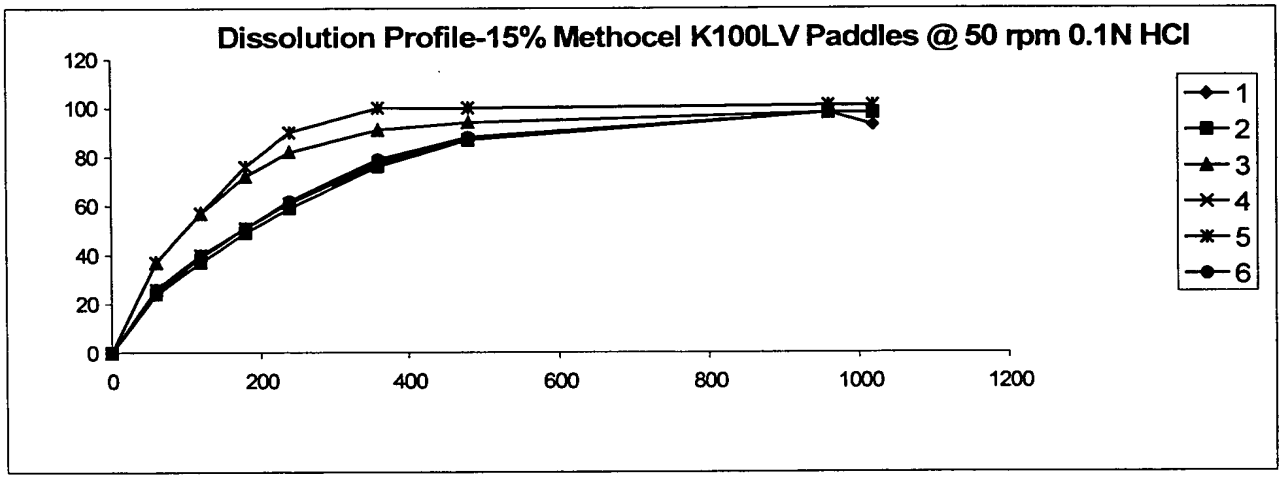


Figure 3c) Matrix tablets with 15% polymer





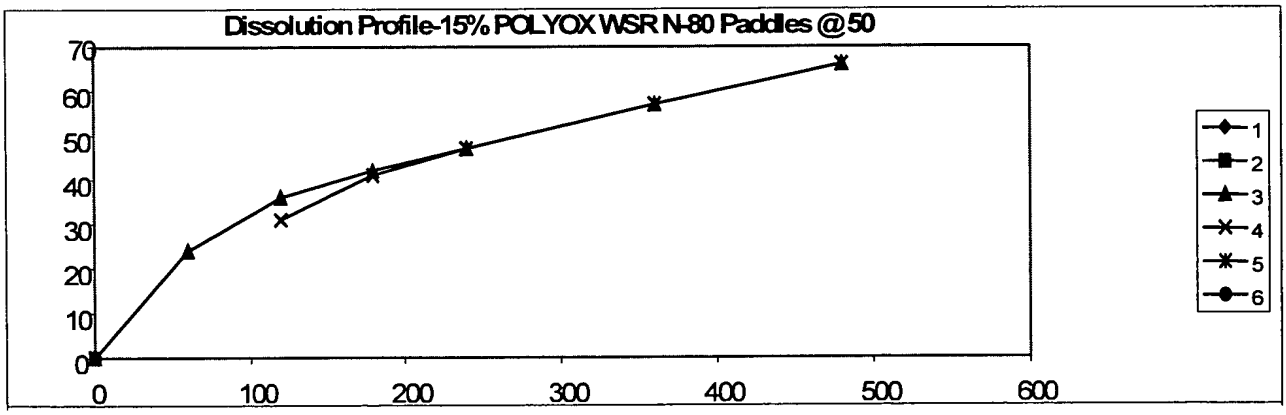
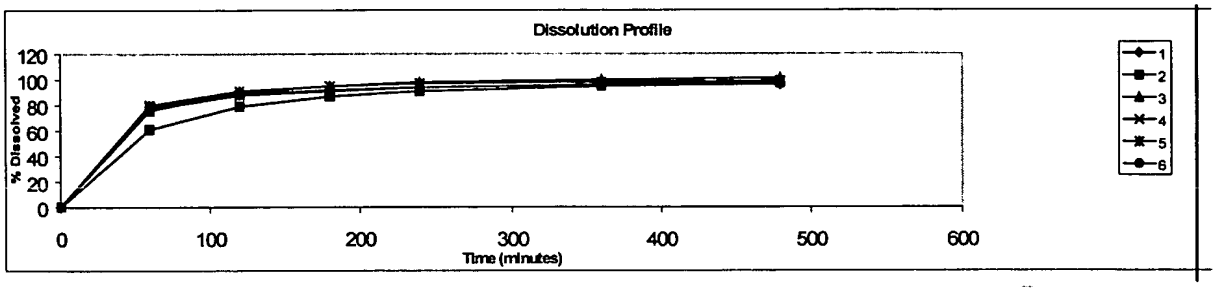


Figure 4 – Dissolution Profile for tablets with 3% and 5% weight gain with a 80%Surelease, 20%Opadry coating.

Lamotrigine Sustained Release

80%Surelease 20% Opadry 3% weight gain



Lamotrigine Sustained Release

80% Surelease 20% Opadry 5 % weight gain